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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/049,868	06/04/2002	Hans Deckmyn	522-1778	2345

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EXAMINER
HADDAD, MAHER M

ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 05/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,868	DECKMYN ET AL.	
	Examiner	Art Unit	
	Maher M. Haddad	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005 and 31 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65,66,70-75 and 80-83* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-66, 70-75, 80-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

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RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 3/07/05 and 3/31/05, is acknowledged.

2. Claims 65-66, 70-75 and 80-83 are pending and under examination in the instant application.

3. Applicant's IDS, filed 3/7/05, is acknowledged.

4. The following new ground of rejection is necessitated by the amendment submitted 3/03/05 and 3/31/05.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 70 and 83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter rejection.

The phrase "at least 80% sequence identity with SEQ ID NO: 4 within the CDR regions as identified in Figure 13" claimed in claim 70, lines 3-4 and claim 83, lines 2-3; represent a departure from the specification and the claims as originally filed.

Applicant's amendment filed 3/7/05 points to the specification at page 7, lines 12-13 and page 9, line 26 to page 10, line 2 for support for the newly added limitations "at least 80% sequence identity with SEQ ID NO: 4 within the CDR regions as identified in Figure 13" as claimed in claims 70 and 83. However, the specification does not provide a clear support for such limitation. It is noted that the specification on page 9, line 26 to page 10, line 2, only discloses the homology may include having at least about 60%, preferably at least 80%, more preferably at least 90% and most preferably at least 95% amino acid sequence identity with the relevant ligand. The homolog were not describe in terms of CDRs. The instant claims now recite a limitation, which was not clearly disclosed in the specification and recited in the claims as originally filed.

7. In view of the amendment filed on 3/07/05 and 3/31/05, only the following rejections are remained.

8. Claims 70-71, 75 and 80-83 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is apparent that the hybridoma LMBP 5108CB, recited in claims 71, 75, and 80-82, that produce the 6B4 antibody is required to practice the claimed invention. As a required element, it must be known and readily available to the public or obtainable by a repeatable method set forth in the specification. If it is not so obtainable or available, the enablement requirements of 35 USC 112, a deposit of the hybridoma, which produces this antibody, may satisfy first paragraph. See 37 CFR 1.801-1.809 for the same reasons set forth in the previous Office Action mailed 11/04/04.

Applicant's statement, filed 3/07/05, does not satisfy the requirement for the deposit of the biological material 6B4 (LMBP 5108CB) under 35 USC § 112, first paragraph. Examiner acknowledges the deposit of 6B4 (LMBP 5108CB) antibody under the terms of the Budapest Treaty on International Recognition of the Deposit of Microorganisms for the Purposes of Patent procedure in partial compliance with this requirement. However, in order to be fully compliant with the requirement, Applicant is also required to assure that all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of a patent in U.S. patent applications (see 37 CFR 1.808 (a)(2) and MPEP 2410-2410.01).

Further, the specification while being enabled for a pharmaceutical comprosition comprising a monovalent antibody fragment which binds in vivo to human platelet glycoprotein GPIb without incurring thrombocytopenia and a pharmaceutically acceptable carrier wherein said fragment is an Fab fragment or a single variable domain or a monovalent antibody fragment which binds in vivo to human platelet glycoprotein GPIb, and prevents the binding of von Willebrand factor to human platelet glycoprotein GPIb which is an Fab fragment or a single variable domain, which inhibits platelet adhesion under high shear conditions; does not reasonably provide enablement for a pharmaceutical composition or a monovalent antibody fragment, wherein the variable region of said fragment comprises a sequence having at least 80% sequence identity with SEQ ID NO: 4 within the CDR regions as identified in Figure 13 in claims 70 and 83 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action mailed 11/04/04.

Applicant's arguments, filed 3/07/05, have been fully considered, but have not been found convincing.

The declaration by Dr. Hans Deckmyn under 37 CFR 1.132 filed 3/7/05 is sufficient to overcome the rejection of claims 65-66, 72-74 based upon 35 U.S.C. 112, first paragraph as set forth in the last Office action which provides evidence that a monovalent antibody fragment of an inhibitory GP1b antibody does not cause thrombocytopenia *in vivo* and hence suitable for use as a pharmaceutical composition.

Regarding claims 70 and 83, applicant points out the claimed antibody fragments must bind to GP1b. Applicant admits that a number of GP1b-binding antibodies are known in the art and can be used to derive the monovalent antibody fragment of the present invention. Applicant contends that methods of obtain monovalent fragments from antibodies are also known in the art and are further detailed, for example on page 14, lines 15-23. Applicant argues that the claims relate to monovalent antibody fragments which bind to GP1b, including variable regions which are at most 20% different within the CDR regions of SEQ ID NO: 3 and 4. Applicant contends that since the CDRs length of VL is 27 and VH is 35 amino acids, a 20% difference corresponds to about 5-7 amino acids where differences may occur. Applicant submits that it is certainly within the skill of the scientist working in the field of antibodies to modify an antibody in the regions outside the CDRs, while ensuring that antigen specificity is not affected. Applicant contends that it cannot be considered undue burden for the skilled person to make limited modifications within the CDRs identified in figure 14, to obtain a monovalent antibody fragment derived from antibody 6B4 which is equally capable of binding GP1b because this binding of the antibody to GP1b can easily be ascertained.

However, (a) applicant only claiming at least 80% sequence identity with SEQ ID NO: 4 within the CDR regions as identified in Figure 13. No claims are drawn to SEQ ID NO: 3 of figure 12. (b) Variation up to 20% within the CDRs of SEQ ID NO: 4 (7^{20}) provide a range of activities, not all which are necessarily predictive of binding in vivo to human platelet glycoprotein GP1b. Therefore, absent the ability to predict which of these antibody fragments would function as claimed, and given that the variations occur on critical regions of the claimed antibody fragments, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue. (c) While applicant claiming the variation within the CDR regions, applicant argues that the skill of the scientist working in the field of antibodies to modify an antibody in the regions outside the CDRs. (d)Applicant has not address the issue raised by the examiner with respect to Rudikoff et al, Panka et al and Amit et al teachings. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff et al (Proc Natl Acad Sci USA 1982 Vol 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. It is unlikely that variable region of the monovalent antibody fragment as defined by the claims which may contain less than the full complement of CDRs from the heavy and light chain variable regions of an GPIb antibody have the required binding function. The specification provides no direction or guidance regarding how to produce monovalent antibody fragments comprising a sequence having at least 80% sequence identity with SEQ ID NO: 4 within the CDR regions as broadly defined by the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone. Panka et al (Proc Natl Acad Sci USA Vol 85 3080-3084 5/88) demonstrate that a single amino acid substiution of serine for alanine results in decreased affinity. In at least one case it is well known that an amino acid residue in the framework region is involved in antigen binding (Amit et al Science Vol 233 747-753 1986).

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 65-66, 70, 72-74 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ward *et al* (1995) (IDS Ref. No. C4), in view of in view of Owens *et al* (1994) and U.S. Pat. No. 4,731,245.

Ward *et al* teach 17 monoclonal antibodies that bind GPIbα epitope of the platelet surface glycoprotein (see table 1 in particular). Ward et al teach that eight antibodies mapped to the N-terminal fragments of gpIba, and these were tested for their ability to block binding of 125I-labelled von Willebrand factor to washed platelets in the presence of ristocetin or botrocetin. Ward et al teach that mAb P014 (epitope 1-282), P024 (epitope 1-282), P073 (epitope 1-282), P074 (epitope 1-282) and P077 (epitope 1-282) completely inhibited vWF binding with wither modulator (see page 1337, 1st col., 3rd paragraph and table I in particular). Finally, Ward et al teach that the inhibitory functions of the CD42b antibodies with their epitopes on gpIba may provide valuable insights into mechanisms of vWF function both in vitro and in vivo (pg 1337, last paragraph in particular).

The claimed invention differs from the reference teaching only by the recitation of a composition comprising a monovalent antibody fragment in claim 65 or a monovalent antibody fragment in claim 72.

Owens *et al* teach the modification of murine antibodies such as a single chain antibody, a Fab fragment or a humanized antibody using monoclonal antibody technology. Owens *et al* further teach humanized antibodies use in therapy of human diseases or disorders, since the human or humanized antibodies are much less likely to induce an immune response. Also, antibody fragments are the reagents of choice for some clinical applications (see the entire document).

The `245 patent teaches a composition comprising the antibody to the PLS antigen, as the active ingredient in association with a pharmaceutically acceptable carrier or excipient. The composition may preferably take the forms suitable for oral administration. Advantageously, the

composition may be formulated in dosage unit form. The amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose (see col., 7 line 63 through col., 8 line 3 in particular).

Claims 70 and 83 are included because the resultant monovalent fragment would contain a variable region encoded by a sequence comprising a sequence having at least 80% sequence identity with SEQ ID NO: 4 within the CDR regions.

While the prior art teachings may be silent as to the "without incurring thrombocytopenia", "which inhibits platelet adhesion and/or inhibits platelet activation under high shear conditions and/or inhibits platelet aggregation under high shear conditions" per se; the product in the reference is the same as the claimed product. Therefore these limitations are considered inherent properties of the resultant antibody.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the monoclonal antibody taught by Ward et al as Fab as taught by the Owens *et al* and place the resultant Fab fragment which binds to platlete glycoprotein GPIbα polypeptide taught by the Ward et al reference in a composition taught by the '245 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because eight antibodies mapped to the N-terminal fragments of gpIba, and these were tested for their ability to block binding of ^{125}I-labelled von Willebrand factor to washed platelets in the presence of ristocetin or botrocetin and because it would further lead to insights into mechanisms of vWF function both in vitro and in vivo. Given that the antibody fragments are the reagents of choice for some clinical applications one ordinary skill in the art at the time the invention was made would be motivated to include such fragments in a composition because the composition can be formulated in dosage unit form. The amount of the active ingredient contained in each dosage unit may be adjusted so as to enable the administration of the antibody at a daily dose as taught by `245 patent.

From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments, filed 3/07/05, have been fully considered, but have not been found convincing.

In contrast to applicant's assertions of the rejection is based upon an "obvious-to-try" standard; it is by now well understood that the ultimate conclusion of law that claimed subject matter as a whole would have been obvious under 35 USC 103 may at times properly be drawn from an inference of fact arising from prior art teachings which could be considered an inference that it would be "obvious to try" that which is claimed. In re O'Farrell, 853 F.2d 894, 7 USPQ 2d 1973 (Fed. Cir. 1988); Contour Saws Inc. v. Starrett Co., 444 F. 2d 433, 170 USPQ 433 (Ct.App. 1977); In re Marzocchi, 439 F. 2d 220, 169 USPQ

367 (CCPA 1977); In re Lindell, 385 F. 2d 435, 155 USPQ 521 (CCPA 1967). The evidence of purported unobvious results of record in this application is insufficient to overcome the inference of fact in this case. Therefore the above claims remain rejected under 35 USC 103 for the reasons above and also those set forth in the previous Office action.

Applicant submits that nothing in the cited references would have suggested to a person of ordinary skill in the art that a monovalent antibody would function in vivo without incurring thromocytopenia. However, Ward et al, Owens and the `245 patent all suggested the in vivo use, for example, Ward et al teach that the inhibitory functions of the CD42b antibodies with their epitopes on gpIba may provide valuable insights into mechanisms of vWF function both in vitro and in vivo (pg 1337, last paragraph in particular). Owens et al teach that antibody fragments are the reagents of choice for some clinical applications. Finally the `245 patent teaches a therapuetic compsotion., the limitation "without incurring thromocytopenia" is an expected properity of the resultant antibody fragments. Further, obviousness does not require absolute predictability but only the reasonable expectation of success. See In re Merck and Company Inc., 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); and In re O'Farrell, 7 USPQ2d 1673 (Fed. Cir. 1988). MPEP 2143.02.

Regarding the argument that Ward has not provided in vivo data, the Examiner notes that Ward suggested the in vivo use. Further, Ward has done nothing different the Applicant's specification with respect to the in vivo data.

Regarding the argument that despite the anti-GP1b antibodies ability to block ristocetin-induced platelet aggregation in vivo, these antibodies would not be considered as suitable pharmaceutical compounds by the skilled person, as these antibodies were also found to induce thrombocytopenia when used in vivo. Applicant directs the examiner's attention to Cadroy et al and Bergmeier et al which both describe the administration of monoclonal antibodies to GP1b or F(ab)2 fragments thereof in vivo in animal models which lead to immediate induction of thrombocytopenia upon administration of the antibody. However, both references used either an intact antibody or a divalent antibody, but not monovalent antibody. Again the resultant antibody fragment of Fab or scFv would not be expected to cause thrombocytopenia.

Regarding Owens applicant submits that Owens does not specifically describe the advantages of monovalent antibody fragmens (Fabs or Fvs) over complete antibodies or F(ab)2 fragments. Contrary to application submissions Owen teaches that antibody fragments can be the reagents of choice for some clinical applications since they have much shorter halflives in vivo compared with intact antibody (see page 149, 2nd col., 1st paragraph in particular). Further, Owens teaches that genetically truncated versions of the antibody may be produced ranging in size from fv through Fab` to F(ab`)2 fragments (see page 150, 1st col., 1st sentence in particular).

In response to applicant's argument that the examiner's conclusion of obviousness is based a discussion of how the references can be pieced together, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the

applicant's disclosure, such a reconstruction is proper. In re McLaughlin , 170 USPQ 209 (CCPA 1971).

The Examiner further notes that, Applicant on page 11, lines 2-3 of the 7/07/05 response admits that any antibody which binds to GP1b is useful for obtaining monovalent antibody fragments having the claimed feature. Further, Applicant on page 11, last two lines admits that a number of GP1b-binding antibodies are known in the art and can be used to derive the monovalent antibody fragment of the present invention. Further, on page 12 lines 1-2 of the response, applicant admits that methods to obtain monovalent fragments from antibodies are known in the art. Furthermore, Applicant's declaration under 1.132, paragraph 4 states that classical antibody against GP1b induces thrombocytopenia, while a monovalent antibody fragment such as a fab fragment of the antibody against GP1b fails to induce thrombocytopenia.

11. No claim is allowed.

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maher Haddad whose telephone number is (571) 272-0845. The examiner can normally be reached Monday through Friday from 7:30 am to 4:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maher Haddad, Ph.D.
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May 19, 2005

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